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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/824,322	04/02/2001	Brenda F. Baker	ISPH-0501	9406

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1638	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

F6

Office Action Summary	Application No. 09/824,322	Applicant(s) BAKER ET AL.	
	Examiner J. Douglas Schultz	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicants' response to the Office action mailed September 9, 2002 has been entered and as per its instructions, claim 4 canceled, and 1 and 6 amended. Applicants' response to the restriction requirement mailed November 1, 2002 has been entered and as per its instructions, claim 25 canceled. Applicants' arguments regarding the restriction requirement have been noted, but are moot in light of the cancellation of claim 25.

Applicant's responses have been considered. Rejections and/or objections not reiterated from the previous office action mailed May 7, 2002 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Response to Arguments

2. Claims 1, and 3-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of colitis and rheumatoid arthritis using antisense compound ISIS 25302, does not reasonably provide enablement for methods of using the full genus of antisense sequences complementary against any portion of TNF-α to inhibit its expression as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention

commensurate in scope with these claims, and is repeated for the same reasons of record as set forth in the Office action mailed May 7, 2002.

Applicants disagree with the examiner that the cited references support the position that application of antisense *in vivo* is highly unpredictable, and argue that when read as a whole, the papers cited "actually teach the potential usefulness of this class of drugs in humans," This argument is not considered convincing. In arguing that the cited references actually teach the potential usefulness of antisense compounds, it is agreed that the *potential* usefulness of such antisense compounds is a prominent theme of said references. However, the fact that antisense technology is still regarded as "potential" speaks to the unpredictable state of the art. Simply because a method has potential does not mean that will work in a predictable fashion. The present articles, in discussing the state of the art, clearly delineate the persistent and unresolved issues in the art relating to predicting the successful *in vivo* use of antisense compounds from *in vitro* studies. To reiterate from the previous Official action, these issues are 1) the crossing of cellular barriers, 2) gaining access to target sites within the folded structure of the mRNA, 3) overcoming maladaptive immune responses, and 4) non-specific binding to proteins of the *in vivo* milieu. Although Applicants have provided one oligo with demonstrated *in vivo* efficacy, Applicants' specification does not provide sufficient guidance to make and use any oligos directed to any region of the instant target, because Applicants have not overcome the substantial unpredictability inherent in the state of the art in regards to successfully making and using such a broad genus of oligos, particularly in light of these unresolved issues, such that one of ordinary

skill in the art could make and use the instant invention without engaging in undue experimentation.

Applicants assert that the references fail to provide a reasonable basis to doubt that the antisense activity observed *in vivo* with one antisense compound of the instant invention would not also occur with other antisense compounds with demonstrated *in vitro* activity. This is not convincing, because the difficulty of moving from *in vitro* to *in vivo* is an underlying theme of all cited articles. For example, Branch et al. states on page 49, far right column, line 25-30, that "[w]ith so many possible sequences to choose from, and the likelihood that *in vitro* studies will not always predict *in vivo* efficacy, straightforward new screening techniques need to be developed for use in cells." Gewirtz et al. indicate (at page 3162, center column, 2nd to last paragraph) that studies of a transfection agent GS2888 complexed with antisense oligos have been successful in cell culture, but studies in primary cell lines are needed, directly implying that tests *in vitro* cannot predict what happens even from one cell line to another let alone in moving from cells in culture to the whole animal. Agrawal et al. devotes the closing section to the unpredictabilities of *in vivo* efficacy, and how the activity of an oligonucleotide in an animal depends on dose, route, administration, disposition in tissues, *in vivo* stability and half-life of the oligo. Such factors cannot be accounted for in *in vitro* screening. This clearly implies that even if one finds an oligo with clear inhibitory capabilities *in vitro*, that it is not currently possible to predict with any reliability its function *in vivo*. Tamm (pg. 493 right column) indicates that the immunostimulatory activity of a phosphorothioate antisense molecule, identical to that claimed by Applicant, is "largely unpredictable." It appears clear from these references that while the

process of drug development may be aided by *in vitro* studies, such *in vitro* studies should not be used as a basis for claiming therapeutic effects in the *in vivo* whole animal. Thus Applicants statement that antisense oligos must be developed through studies that progress logically from activity in cells to activity in animals and humans is agreed with. However, Applicant has not neither exemplified such a progression for the broad genus claimed, nor provided a means of developing such oligos through said progression without engaging in undue experimentation.

In the same vein, Applicants argue that it is a fundamental principle of drug development that data from whole cell studies (*in vitro*) are directly applicable to *in vivo* activity, and further, that when one compound of a class of compounds have been shown to be active *in vivo*, it is a general principle of pharmacology that other compounds with similar *in vitro* activity will also be active *in vivo*. These arguments are not convincing. This fundamental principle, if it applies to other systems, is not appropriate for antisense technology, because although oligos directed to the instant target share common chemical structure based upon the four RNA monomers, it is the *sequence* of such oligos, not their monomeric chemical structure, that confers antisense inhibitory activity. As a result, although these oligos belong to the same class of drugs, demonstrated *in vivo* success with one oligo does not make *in vivo* success with other oligos predictable by any means, because the sequence that the RNA monomers are arranged in within the antisense compound determines how the oligo behaves in relation to both antisense inhibition and the four mechanistic problems listed above. Each antisense oligo would be expected to have its own unique problems gaining cellular access, and target access, and each antisense oligo would be expected to elicit a unique immune response, and to bind unpredictably to plasma and

cellular proteins, that cannot be predicted *a priori* from results obtained *in vivo*. Accordingly, because one oligonucleotide has been provided by Applicant that demonstrates *in vivo* effect does not indicate that Applicants have provided enabling disclosure for any oligonucleotide directed to any region of the instant target as broadly claimed, because one would have to engage in undue experimentation in order to successfully make and use compounds such compounds *in vivo*.

Furthermore, Applicants' assertion that the statements of Crooke et al. supporting unpredictability don't apply to the instant situation because data from one antisense compound has been shown to support extrapolating data from *in vitro* studies to the *in vivo* whole animal is not convincing, for the reasons outlined above. Applicants' do not provide enabling disclosure for predicting the successful extrapolation from *in vitro* data to the *in vivo* whole animal using related antisense compounds directed to the same target, because each sequence is unique, which in turn drives its behavior *in vivo*.

Applicants' quotation of Crooke et al., "...numerous well-controlled studies have been reported in which antisense activity was conclusively demonstrated [*in vitro*]" is not considered relevant to the enablement rejection of the previous Office action, because said rejection conceded enablement for *in vitro* studies. Indeed, antisense inhibition is routinely performed by those of skill in the art *in vitro*, and the previous Office action granted that such inhibition is enabled by the present specification. What is pertinent to the present situation is whether the successful *in vivo* usage of one antisense oligo thus enables Applicants for the successful use of

the broad genus of claimed antisense oligos *in vivo*. For the reasons outlined above, because each oligo has its own unique sequence that both confers inhibitory activity but also its own unique problematic biochemical interactions within the organism, Applicants successful demonstration of one antisense oligo *in vivo* does not provide enablement for the broad genus of such antisense oligos *in vivo*.

Applicants argument that none of the referenced citations indicate that extrapolation from *in vitro* data on antisense compounds to *in vivo* effects is unpredictable is not considered convincing. The references provided provide explicit indications of the high level of unpredictability in critical elements of antisense-mediated gene inhibition, such as those passages quoted above. In further example, Crooke et al., on page 3, first paragraph: "Finally, extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man that demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies..." According to the reasoning in this passage, it follows that any oligo which is taken up by a cell *in vitro*, even if it proceeds to inhibit the target, that no meaningful prediction can be made as to whether the oligo will ever be taken up by cells *in vivo*; such uptake *in vivo* being a prerequisite for subsequent target inhibition as understood by one of skill in the art.

While the articles present the challenges inherent in attaining any experimental success using antisense oligos, as stated by Braasch, "clinical development presents the pinnacle for the

capabilities for the scientist to accurately predict and design useful molecules for antisense technology because potency, specificity, target selection, and pharmacokinetic properties must be optimal." Given that these references all imply or explicitly state the challenges in attaining any success, let alone that experienced *in vivo*, these references, when read as a whole, support the concept that the state of the art of predicting *in vivo* antisense inhibition from *in vitro* studies is unpredictable. In summary, Applicants' arguments that none of these papers explicitly disclose a high level of unpredictability in applying *in vitro* results to *in vivo* situations is not convincing, because the underlying theme of these papers is a discussion of the problems encountered in using antisense inhibition technology in more meaningful, i.e. *in vivo*, situations.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
March 25, 2003